REMARKS

I. Status Summary

The instant application was subject to a final rejection as set forth in a Final Official Action dated May 31, 2002. Applicants filed a response, including a Notice of Appeal and Amendment After Final, on November 27, 2002. In an Advisory Action dated December 11, 2002, applicants were informed that the Amendment After Final had been entered, that certain rejections had been overcome, but that others were maintained. The present Amendment is filed in conjunction with a Request for Continued Examination (RCE).

Claims 44-54 are pending in the current application. Claims 44-48 and 52 have been amended for clarification. Support for the amendment to claim 44 can be found throughout the specification as filed, including particularly at page 8, lines 12-14, page 20, lines 15-17, and in Example 2. Support for the amendments to claims 47 and 48 can be found throughout the specification as filed, including particularly on page 11, lines 13-15 ("a feeder matrix can be derived from or provided by the organ or tissue in which the primordial germ cells are located, e.g., the gonad.") and page 10, lines 22-24 ("avian embryonic gonadal cells comprising primordial germ cells...may be collected from, for example, the avian embryonic genital ridge or gonad"). Further support for the amendments to claims 44, 47, and 48 can be found on page 10, lines 3-8 (avian embryos from which cells are obtained for carrying out the present invention are preferably after stage 14, more preferably stage 14 to stage 45, even more preferably stage 15 to stage 31, including stages 17, 18, 19, 20, and 21, and most preferably stage 27 to 30 of development on the Hamburger & Hamilton (H&H) staging system").

Claims 49 and 50 have been withdrawn. New claim 55 has been added. Support for new claim 55 can be found throughout the subject application as filed, including particularly at page 4, lines 18-20; page 8, lines 20-22; page 12, lines 4-8; and Example 1.

No new matter has been added by the amendments.

II. 35 U.S.C. § 112, First Paragraph Issues Outstanding in the Advisory Action Dated December 11, 2002

In an Advisory Action dated December 11, 2002 (hereinafter the "Advisory Action"), the Patent Office indicated that amendments offered in an After Final Amendment presented in the prosecution of the application prior the filing of the present Request for Continued Examination failed to overcome several rejections of the claims under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse the assertions of the Patent Office in the Advisory Action, and submit the following comments.

New Matter Rejections

According to the Patent Office, claim 44 is not supported by the specification because although page 11, lines 11-12 states that the culture of the invention may include a feeder matrix, and lines 16-23 state that the feeder cells may be "preconditioned", the citations do not contemplate combining PGCs and stromal cells collected from an embryo after state 14 with the "preconditioned feeder matrix". Applicants respectfully direct the Patent Office's attention to the Examples, particularly Example 2, in which is it stated that PGCs were grown on different numbers of STO feeder cells in culture. Furthermore, this same Example indicates that "the survival and proliferation of the gonadal PGCs was affected by the quality of the STO feeder layer, the number of STO cells seeded, preconditioning of the STO feeder layer, and the number of gonadal cells initially seeded." Page 20, lines 15-17. Gonadal PGCs are isolated in conjunction with stromal cells. See page 8, lines 12-14. Thus, it is clear that PGCs and stromal cells that are collected after Hamburger & Hamilton (hereinafter "H & H") stage 14 and cultured on a preconditioned feeder matrix are supported by the specification as filed. The entire specification discloses the culture of avian PGCs, isolated in conjunction with stromal cells, with feeder cells, which can comprise a preconditioned feeder matrix. The mere fact that the specification does not disclose in a single sentence that post-stage 14 PGCs along with stromal cells can be cultured with a preconditioned feeder matrix cannot and

should not be considered a failure of disclosure of this particular combination. Accordingly, applicants respectfully request that the Patent Office withdraw the contention that the specification as filed does not contemplate culturing PGCs and stromal cells with a preconditioned feeder matrix.

Similarly, the Patent Office contends that while page 10, line 17 suggests isolating avian cells having an ES cell phenotype from avian gonadal cells comprising PGCs collected from an avian embryo, the citation does not suggest combining avian stromal cells collected from an embryo with the PGCs or that the embryo was later than stage 14. Again, the specification explicitly discloses that avian gonadal cells comprising PGCs isolated in accordance with the present invention can also comprise stromal cells. As disclosed on page 8, lines 12-14, a PGC preparation will have stromal cells in it. Furthermore, page 10, lines 3-8 state that avian embryos from which cells are obtained for carrying out the present invention are preferably after stage 14, more preferably stage 14 to stage 45, even more preferably stage 15 to stage 31, including stages 17, 18, 19, 20, and 21, and most preferably stage 27 to 30 of development on the Hamburger & Hamilton (H&H) staging system. As such, applicants respectfully submit that the specification discloses a culture of avian stromal cells and PGCs collected from an embryo later than stage 14 (H&H).

It has never been necessary that the specification recite in one sentence that which is clearly described in the specification. According to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, First Paragraph, "Written Description" Requirement (66 Federal Register 1099, 2001; hereinafter "The Guidelines") "if a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." Id. at page 1106. In this case, every nuance is explicitly described, and yet the Patent Office has maintained these rejections without any support other than conclusory statements that are believed to be contradicted by the specification.

The Patent Office has also asserted that the specification does not support the breadth of combining any avian PGCs and avian stromal cells isolated from an avian embryo. As discussed above, stromal cells and PGCs can be co-isolated as described on page 8, lines 12-14. However, in an effort to clarify this point, claim 44 has been amended to recite a sustained culture of undifferentiated avian cells expressing an embryonic stem cell phenotype, comprising a preconditioned feeder matrix; conditioned media; and avian primordial germ cells and stromal cells, wherein the avian primordial germ cells and stromal cells are isolated together from an embryo later than stage 14 (H&H) and grown in the sustained culture to produce undifferentiated avian cells expressing an embryonic stem cell phenotype. Support for this amendment can be found on page 8, lines 12-14.

The Patent Office further asserts that the citation on page 10, line 14, is limited to isolating cells from the embryonic gonads, not isolating cells from anywhere in the embryo as broadly encompassed in claim 44. Contrary to the Patent Office's contention, however, claim 44 recites that the sustained culture comprise avian primordial germ cells and stromal cells collected from an avian embryo later than stage 14 (H&H). As such, the isolation of cells from the embryo is from an area that has primordial germ cells. One such area is the embryonic gonads. Another is the genital ridge as disclosed on page 10, lines 22-24, in which it is stated that primordial germ cells may be collected from the avian genital ridge or gonad. The Patent Office appears to be impermissibly importing a limitation into the claims. Applicants respectfully submit that claim 44 recites that the culture comprise avian primordial germ cells, and that one of ordinary skill in the art would understand the metes and bounds of this element.

The Patent Office also contends that the citation on page 10, line 14 is limited to collecting "gonadal PGCs and stromal cells", not any PGCs as broadly encompassed in claim 44. However, as discussed above, the specification discloses isolating PGCs from the avian genital ridge or gonad. See page 10, lines 22-24. In order to facilitate prosecution of this case, however, applicants have amended claim 44 to recite a sustained culture of undifferentiated avian cells expressing an

embryonic stem cell phenotype, comprising a preconditioned feeder matrix; conditioned media; and avian primordial germ cells and stromal cells, wherein the primordial germ cells and stromal cells are isolated together from the genital ridge or gonad of an avian embryo later than stage 14 (H&H) and grown in the sustained culture to produce undifferentiated avian cells expressing an embryonic stem cell phenotype. The amendment is directly supported by the specification at page 10, lines 22-24.

The Patent Office next contends that page 11, lines 3-10 does not teach that stromal cells are genital ridge cells. However, as noted above, during the isolation of primordial germ cells from avian embryos, stromal cells are also isolated. See page 10, lines 12-14 of the subject application. Accordingly, when PGCs are isolated from, for example, genital ridge cells, the stromal cells isolated in conjunction with the genital ridge PGCs will be genital ridge stromal cells. Applicants respectfully submit that according to The Guidelines, a patent specification "need not teach, and preferably omits, what is well known in the art". The Guidelines at page 1103, quoting Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534 (Fed. Cir. 1987). Applicants submit that when read in light of the specification as a whole, one of ordinary skill in the art would understand clearly that the stromal cells isolated in conjunction with PGCs isolated from the genital ridge are genital ridge cells because they come from the genital ridge. The Patent Office has offered no evidence or technical reasoning why one of ordinary skill in the art would not understand the metes and bounds of this recitation.

The Patent Office next contends that while page 11, lines 13-15 support a feeder matrix derived from the gonad, the citation does not suggest the matrix is preconditioned when derived from the gonad or that the cells isolated are gonadal (as in claim 47). The claim recites a preconditioned feeder matrix that is derived from gonadal cells. In other words, a feeder matrix derived from the gonad is established, which the Patent Office concedes is supported by the specification. Next, this feeder matrix is preconditioned as described in the specification, for example, as described on pages 11 and 12, wherein it is disclosed that:

> By the term "preconditioned" it is meant that the feeder matrix is cultured in the presence of media for a period of time prior to the depositing of gonadal cells comprising primordial germ cells in contact with the feeder matrix, e.g. a time sufficient to initiate and establish production of, for example, growth factors or other factors by the feeder matrix. As disclosed in the Laboratory Examples, a feeder matrix is preconditioned by culturing the feeder matrix by itself for one to two days prior to the depositing of gonadal cells comprising primordial germ cells in contact with the feeder matrix.

See page 11, line 19 to page 12, line 2 of the subject application. Thus, there is no requirement in the language of the claim that the feeder matrix be preconditioned when derived from the gonad.

Additionally, the specification explicitly states on page 11, lines 13-15 that "a feeder matrix can be derived from or provided by the organ or tissue in which the primordial germ cells are located, e.g., the gonad." Thus, it is respectfully submitted that the citation explicitly discloses that the cells are gonadal – that is, from the gonad. This is believed to rebut the Patent Office's assertion that "gonadal cells have a different scope than cells of the gonad because "gonadal cells" may be limited to cells having gonadal function while cells derived from the gonad can be cells that provide gonadal function as well as structural cells that do not provide gonadal function." See Advisory Action, Continuation of 5.

The Patent Office next contends that page 11, lines 13-15 and page 19, lines 14-16, do not suggest isolating feeder matrix from the "genital ridge" (claim 48). Page 11, lines 13-15 state that "a feeder matrix can be derived from or provided by the organ or tissue in which the primordial germ cells are located, e.g., the gonad." Furthermore, the specification discloses that "avian embryonic gonadal cells comprising primordial germ cells...may be collected from, for example, the avian embryonic genital ridge or gonad". Page 10, lines 22-24. If "a feeder matrix can be derived from or provided by the organ or tissue in which the primordial germ cells are located", and "primordial germ cells...may be collected from, for example, the avian embryonic genital ridge", then it is believed to be clear that a feeder matrix can be derived from the avian embryonic genital ridge".

The Patent Office next contends that page 10, lines 1-9, and page 11, lines 13-15, do not contemplate the feeder matrix isolated from "gonadal cells" or "genital ridge" is after stage 14. Based upon the arguments set forth herein above, it is believed that applicants have established that a feeder matrix can be isolated from gonadal cells and/or the genital ridge. Additionally, page 10, lines 3-8 states clearly that avian embryos from which cells are obtained for carrying out the present invention are preferably after stage 14, more preferably stage 14 to stage 45, even more preferably stage 15 to stage 31, including stages 17, 18, 19, 20, and 21, and most preferably stage 27 to 30 of development on the Hamburger & Hamilton (H&H) staging system.

The Patent Office next contends that page 14, lines 4-7, does not contemplate the ES cell phenotype is sustained for at least one or two months (claims 53-54). According to the Patent Office, the citation instead contemplates culturing PGCs that develop into cells having an ES phenotype and that the culture is sustained for one or two months. The Patent Office offers no support for the contention that the ES cell phenotype is not sustained for the entire time that the culture is sustained, i.e. one or two months. The Patent Office contends that the citation is not limited to maintaining the ES cell phenotype for one or two months and does not teach culturing cells after they have the ES cell phenotype. Applicants have taught that culturing the cells as described results in a culture of avian cells having an ES cell phenotype that can be sustained for at least one or two months.

In summary, applicants respectfully submit that the Patent Office has not carried its burden regarding the new matter rejections entered in the instant application. As a result, applicants respectfully request that the new matter rejections be withdrawn, and the claims be allowed at this time.

Enablement Rejection

The Patent Office asserts that the specification does not enable claims 53 and 54 related to the culture of PGCs and feeder cells sustained for one or two months. According to the Patent Office, Examples 1-4 and page 14, lines 4-5 do not enable

the culture of PGCs and feeder cells for one or two months. Applicants respectfully traverse this rejection.

As a matter of Patent Office practice, the burden rests upon the Patent Office to establish a prima facie case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to the invention described and claimed in applicants' presumptively enabling patent application. See In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

The Patent Office contends that the specification of the present U.S. patent application does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims. However, no specific scientific or other factual basis in support of this contention has been presented in either the Official Action or the Advisory Action.

Applicants submit that the Patent Office has not met its burden, as is required under In re Marzocci. Rather, the Patent Office has offered only a series of conclusory statements, contending that "given the teachings in the art taken with the teachings in the specification, it would have required one of skill undue experimentation to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as broadly claimed". Official Action dated May 31, 2002, page 4. Applicants respectfully submit that a prima facie case of a lack of enablement under 35 U.S.C. §112, first paragraph, has not been made.

Indeed, 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, and this requirement has clearly been met. Accordingly, claims 1-15 are believed to be in compliance with 35 U.S.C. §112, first paragraph. Claim 4 has been canceled, and thus the rejection of claim 4 has been rendered moot. Withdrawal of this rejection of claims 1-3 and 5-15 is respectfully requested.

However, assuming arguendo that the Patent Office has made a prima facie case of a failure to comply with 35 U.S.C. §112, first paragraph, applicants respectfully submit the following. The Patent Office's primary contention in support of the rejection under 35 U.S.C. §112, first paragraph, appears to be that undue

experimentation would be required to use the entire scope of the claimed invention. Official Action, page 2. It also appears that it is the Patent Office's position that 35 U.S.C. §112, first paragraph, requires the presentation of working examples.

Applicants respectfully submit that an inappropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, has been adopted. The appropriate standard is that the claimed invention must be enabled so that a person skilled in the art can make and use the invention from the disclosures of the specification, coupled with information known in the art, without "undue experimentation". In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988).

In the Official Action dated May 31, 2002, the Patent Office contends that "given the teachings in the art taken with the teachings in the specification, it would have required one of skill undue experimentation to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as broadly claimed". Official Action, page 4. Indeed, while it might require considerable experimentation to practice the instant invention, the quantity of experimentation to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." In re Wands, 8 U.S.P.Q. 2d at 1404 (citing In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. U.S. v. Telectonics, Inc., 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

While the presence or absence of working examples is one consideration in the overall evaluation of enablement, working examples are not required under 35 U.S.C. §112, first paragraph, to comply with the enablement standard presented therein. Indeed, the M.P.E.P. states that the specification need not contain an

example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. M.P.E.P. §2164.02. The M.P.E.P. also states that a lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. Id. (emphasis added).

In addition, the Laboratory Examples disclose precise experimental parameters to enable one skilled in the art to practice the invention. As conceding by the Patent Office, Example 1 teaches insolating gonadal PGCs and stromal cells. Example 2 teaches culturing gonadal PGCs and STO feeder cells. Example 3 teaches culturing gonadal PGCs and preconditioned feeder cells. And Example 4 teaches culturing gonadal PGCs and different concentrations of STO feeder cells. Thus, the level of detail disclosed in the Laboratory Examples and in the specification proper provides ample and specific guidance for one skilled in the art to practice the invention. Accordingly, applicants respectfully request that the present rejection be withdrawn and that claims 1-3 and 5-15 be allowed at this time.

Further, the disclosure of the instant U.S. patent application as filed also provides specific guidance for isolating and culturing chicken cells, including particularly at page 4, lines 18-20; page 8, lines 20-22; page 12, lines 4-8; and Example 1. New claim 55 has been added, which recites chicken cells. For the reasons set forth herein above, allowance of new claim 55 is respectfully requested.

III. 35 U.S.C. § 112, Second Paragraph, Issues Outstanding in the Advisory Action Dated December 11, 2002

The Patent Office has maintained all its rejections under 35 U.S.C. § 112, second paragraph, "for the reasons of record". These rejections are respectfully traversed.

It is respectfully submitted that the specification must be viewed from the perspective of the skilled artisan. According to the Court of Appeal for the Federal Circuit (hereinafter the "Federal Circuit"), "the definiteness inquiry focuses on whether

those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification". See Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986). Furthermore, claim language need only "reasonably apprise those skilled in the art" as to the scope of the claim, and be "as precise as the subject matter permits". See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). And finally, the Federal Circuit has stated: "if the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more". Id.

Applicants respectfully submit that the definitions proposed by the Patent Office for terms used in the present application are believed to be contrary to the understanding of the skilled artisan. For example, the Patent Office maintains that a stromal cell is "a part of an organ or other structure" because that is the definition of "stromal" (but note, not "stromal cell") found at http://cancerweb.ncl.ac.ul/cgi-bin/omd?stromal. Applicants have argued that the term "stromal cell" is "a connective tissue cell of an organ found in loose connective tissue" as defined at http://cancerweb.ncl.ac.ul/cgi-bin/omd?stromalcells. Thus, the Patent Office appears to reject the precise definition of "stromal cell" that is presented at the website it referenced in favor of the less precise definition for "stromal". Moreover, the chosen definition leads the Patent Office to conclude that "any cell isolated from an animal is a stromal cell". See Official Action dated May 31, 2002 at page 6. The Patent Office appears to be asserting that one of ordinary skill in the art would agree with the statement that "any cell isolated from an animal is a stromal cell".

Applicants respectfully submit that one of ordinary skill in the art would understand the term "stromal cell" to refer to a cell that is not merely "a part of an organ or other structure" as asserted by the Patent Office, but more precisely to refer to a "connective tissue cell of an organ found in loose connective tissue", such as that found in the bone marrow (see Van Damme et al., "Bone marrow stromal cells as targets for gene therapy", Curr Gene Ther 2(2):195-209, 2002; Bubnic et al., "W/W(v) marrow stromal cells engraft and enhance early erythropoietic progenitors in

unconditioned SI/SI(d) murine recipients", Bone Marrow Transplant 30(12):867-72, 2002) or in the vicinity of migrating primordial germ cells (see Doitsidou et al., "Guidance of primordial germ cell migration by the chemokine SDF-1", Cell 111(5):647-59, 2002). It is thus respectfully submitted that the Patent Office has not met its burden of establishing a lack of compliance with 35 U.S.C. § 112, second paragraph, through the use of the phrase "stromal cell" in the claims.

The Patent Office also asserts that a "germ cell" is "a gamete or one of its antecedent cells". Applicants understand that in this context, an "antecedent cell" would be considered a cell that is characterized by a restricted differentiation potential to produce gametes, for example, the cells of the male and female gonads that differentiate exclusively into sperm and ova, respectively. As such, applicants respectfully submit that the term "germ cell" would be understood to include spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa in the male, and the corresponding cell types in the female. The term "germ cell" might also be understood to include primordial germ cells. It appears that the Patent Office is implying that ES cells are gametes because an ES cell can differentiate into a gamete. The specification has to be read from the perspective of one of ordinary skill in the art, and it is respectfully submitted that one of ordinary skill in the art would not understand the term germ cell to include all cells that had any potential to develop into a gamete, as this would include a fertilized one-cell embryo. Applicants respectfully submit that one of ordinary skill in the art would not consider a one-cell embryo a germ cell, and it is similarly respectfully submitted that one of ordinary skill in the art would not view an ES cell as a gamete.

Claim 44 has been rejected upon the contention that the phrase "undifferentiated avian cells expressing an embryonic stem cell phenotype" is unclear. The specification clearly defines the ES cell phenotype as having a large nucleus, prominent nucleolus, and little cytoplasm. Additional functional characteristics are also provided at page 9, lines 15-23 wherein common immunological markers and the ability to differentiate extensively are described. That is, undifferentiated avian cells expressing an embryonic stem cell phenotype are

pluripotent. As the standards for definiteness are measured through the eyes of one of ordinary skill in the art, applicants respectfully submit that this definition provides all the information that is required for one of ordinary skill in the art to understand the metes and bounds of the claims.

It is further asserted that the phrase "preconditioned feeder matrix" is unclear. The term "preconditioned" is clearly defined at page 11, line 20 of the subject U.S. patent application file wherein it states that the feeder matrix is cultured in the presence of media for a period time prior to the depositing of gonadal cells comprising primordial germ cells in contact with the feeder matrix, e.g. a time sufficient to initiate and establish production of, for example, growth factors or other factors by the feeder matrix. It is further asserted that the term "preconditioned" is a term understood by those of skill in the art, and the use of the term here is consistent with its use in the art. Applicants respectfully submit that this guidance would be sufficient for one of ordinary skill in the art to understand the metes and bounds of the use of the phrase "preconditioned feeder matrix" in the claims. Accordingly, applicants respectfully submit that the term "preconditioned feeder matrix" in the claims is definite and would be understood by one of ordinary skill in the art.

It is further asserted that the phrase "conditioned media" is indefinite. Applicants respectfully submit that the phrase "conditioned media" would be readily recognized by one of ordinary skill in the art in that it refers to media that has been conditioned by the addition of growth factors or other reagents. Indeed BRL conditioned media is a commercially available product. Applicants have amended the claims to recite that "BRL" is meant to refer to Buffalo Rat Liver. This amendment is supported by the specification in that a source of the BRL conditioned media is described in the specification at page 13, lines 12-15. Additionally, the Table of Abbreviations list BRL as an abbreviation for Buffalo Rat Liver. Accordingly, applicants respectfully submit that the recitation of the phrase "conditioned media" in the specification is definite and would be understood by one of ordinary skill in the art.

It is further asserted that the phrase "(H&H)" is indefinite, upon the contention that it is unclear whether (H&H) is intended to further limit the stage or if it is a method of staging as required in the claim. The specification has been amended to correct a typographical error, wherein "Hamburger" appears as "Hanburger". Applicants respectfully submit that, as defined in the specification at page 10, lines 7-8, the term "(H&H)" refers to the Hamburger & Hamilton scale, which is an art-recognized staging scale. Thus, the usage of this term is meant to describe the stage of embryo from which the cells are isolated. The H&H scale is to be contrasted with the Eyal-Giladi & Kochav (hereinafter "EGK") scale, which uses Roman numerals to denote the stages, most of which are before the egg is laid. Accordingly, applicants respectfully submit that the recitation of the phrase "(H&H)" in the specification is definite and would be understood by one of ordinary skill in the art.

It is further asserted that the metes and bounds of a matrix "derived" from a gonadal or genital ridge cell cannot be determined. In this regard, applicants have understood this rejection to refer to claims 47 and 48, which recite that the preconditioned feeder matrix is derived from avian gonadal cells and from avian genital ridge cells respectively. Described at page 11, lines 13-15, the feeder matrix can be derived from or provided by the organ or tissue in which the primordial germ cells are located, e.g., the gonad. Thus, the term "derived from" simply means that the feeder matrix is prepared using gonadal cells. Applicants respectfully submit that the usage of the term "derived from" in the context of a preconditioned feeder matrix would be understood by one of skill in the art. Therefore, applicants respectfully submit that the term "derived" is definite as used in claims 47 and 48. However, in an effort to advance the prosecution of the instant application, applicants have amended claims 47 and 48 to replace the term "derived from" with "isolated from".

It is further asserted that it is unclear how PGCs isolated from an embryo later than stage 14 are distinguished from PGCs isolated from a stage X or stage 14 embryo. Applicants respectfully note that the H&H system, which uses stage numbers in Arabic numerals, is a more precise staging system than the EGK staging system, which uses stage numbers in Roman numerals. That is, there are more

divisions in the H&H staging system so that a stage later than 14 in Arabic numerals is quite different than a stage later than XIV in Roman numerals. Additionally, the EGK staging system refers to pre-gastrulation stages of embryonic development. Stage XIV (EGK) thus occurs at least 40-45 hours before stage 14 (H&H). Applicants respectfully submit that in the present claims, PGCs isolated from the embryo later than stage 14 (H&H) are capable of becoming embryonic stem cells, i.e., they express an embryonic stem cell phenotype. Thus, they can be cultured to provide pluripotent cells. The primordial germ cells in the claimed cultures are isolated from the embryo that is later than stage 14 on the H&H scale. Applicants respectfully submit that the stage refers to the embryo, not the cells, and one of ordinary skill in the art can easily distinguish a stage 14 embryo from a stage X embryo or a stage XIV embryo. Applicants respectfully submit that it is improper for the Patent Office to "read out" one of the elements of the claims by asserting that a PGC isolated from a later than stage 14 embryo is equivalent to a PGC isolated from a stage X embryo, a stage XIV embryo, or even a stage 14 embryo.

It is further asserted that the metes and bounds of the term "sustained" in claims 53 and 54 are indefinite. As described in the present U.S. patent application as filed at page 14, lines 4 – 7, the avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of a primary cultures of cells from an unincubated avian embryo. Thus, applicants respectfully submit that claims 53 and 54 clearly recite that the cells can be cultured for at least one or two months, respectively. It appears that the current rejection is based on an unsupported assertion by the Patent Office that the culture cannot be maintained for at least one month (claim 53) or two months (claim 54). Thus, applicants respectfully request the withdrawal of this rejection.

In view of the foregoing, applicants respectfully submit that claims 44 through 54 are in compliance with 35 U.S.C. § 112, second paragraph. Accordingly, withdrawal of the rejection of claims 44 - 54 under 35 U.S.C. § 112, second paragraph, and allowance of the claims is respectfully requested.

IV. Response To First Rejection Under 35 U.S.C. § 102(b)

Claims 44 - 54 have been rejected under 35 U.S.C. § 102(b) as anticipated by Allioli et al., Devel. Biol., 165:30-37 (1994) (hereinafter "Allioli"). Allioli is asserted to teach the isolation of chicken cells from gonad of a stage 27 to 28 embryo and culturing the cells in media. It is further asserted that the sample contained PGCs as well as fibroblasts that created a feeder layer in culture. It is further asserted that the PGCs of Allioli have an ES cell phenotype because both PGCs and ES cells are germ cells. It is further asserted that Allioli teaches adding steel factor, LIF and FGF to the culture. Applicants have carefully considered this rejection and the basis for this rejection, and respectfully traverse the same as follows.

It is well settled that for a reference to anticipate a claim under 35 U.S.C. § 102(b), the reference must disclose each and every element of the claim. Applicants respectfully disagree with the Patent Office's characterization of PGCs and ES cells as equivalent because both PGCs and ES cells are germ cells. In contrast to the Patent Office's assertion, ES cells are not germ cells, as germ cells are defined as the reproductive cells in multicellular organisms (see definition at http://cancerweb.ncl.ac.uk/cgi-bin/omd?germcells). ES cells are in fact not reproductive cells at all, as that term is usually understood by one of ordinary skill in the art. ES cells are isolated from a stage of embryonic development (a blastula) that occurs before any cells have differentiated into a cell type that would plausibly be understood as a reproductive cell. Furthermore, an aspect of the present invention is to provide pluripotent or totipotent undifferentiated cells expressing an embryonic stem cell phenotype from primordial germ cells. Thus, the undifferentiated avian cells expressing an embryonic stem cell phenotype recited in claim 44 have pluripotent or totipotent characteristics, whereas primordial germ cells normally develop only into the gametes of the bird. Accordingly, applicants respectfully submit that the recitation presented in claim 44 is not anticipated by the teachings of the Allioli reference.

Claims 45 – 54 ultimately depended upon patentably distinguished claim 44. Accordingly 45 – 55 are believed to be patentably distinguished from the Allioli

reference in view of this distinction. Withdrawal of this rejection is respectfully requested. Allowance of claims 45 – 54 is also respectfully requested.

V. Response to Rejection of Claims 44 – 54 under 35 U.S.C. § 102(b) based upon Chang

The Patent Office has rejected claims 44 – 54 under 35 U.S.C. § 102(b) as being anticipated by Chang, Cell Biol. Intl 21:495-499 (1997) (hereinafter "Chang 1997") for the reasons set forth at paragraph 7, of pages 9 and 10 of the Official Action. Applicants have carefully considered this rejection and respectfully traverse the same as follows.

Applicants initially wish to point out that the Patent Office appears to be basing this rejection on the disclosures of at least two references: the Chang 1997 reference cited above, as well as a reference cited within Chang 1997, namely Chang et al., Cell Biol Intl 19: 143-149 (1995). Applicants respectfully submit that a 102(b) rejection should not properly be based upon more than one reference. Accordingly, applicants request that this rejection under 102(b) of claims 44-54 be withdrawn and the claims be allowed at this time.

In an abundance of caution, however, applicants wish to address the bases of the Patent Office's contentions, and do so by submitting the following remarks. Claim 44 recites that the PGCs are isolated from an embryo later than stage 14. The Patent Office asserts that this element does not bear patentable weight because it does not distinguish the structure or function of the PGCs within the culture for those taught by the Chang 1997 journal article. Applicants respectfully note that prior to the invention of the present application, it was not perceived to be possible to provide a sustained culture of avian cells expressing a pluripotent embryonic stem cell phenotype that could be derived from PGCs isolated from a later than stage 14 embryo. Indeed it was believed that PGCs isolated from later than stage 14 embryos were destined for terminal differentiation into germ cells instead of other tissues.

Moreover, PGCs are more easily isolated from later stages. Additionally, applicants respectfully submit that PGCs isolated from a later than stage 14 (H&H)

embryo are distinguishable from PGCs from the blood of day 2 (stage 13-14) embryos because, by definition, stage 13-14 is not "later than stage 14". Accordingly, the PGCs isolated from embryos later than stage 14 are believed to be patentably distinguishable from the disclosure of the Chang reference(s). Accordingly, a withdrawal of the rejection of claim 44 based on Chang is respectfully requested.

Applicants respectfully submit that the Patent Office's characterization of the teachings of Chang 1997 that PGCs isolated from stage 27 – 28 embryos have an ES cell phenotype because they are germ cells is not accepted in the art. As mentioned above, ES cells are not germ cells. Additionally, an ES cell phenotype as recited in the subject application and in claim 44 pertains to a pluripotent cell that is capable of differentiation into any tissue including, but not limited to germ cells. Accordingly, claim 44 is believed to be further distinguished from the teachings of the Chang 1997 journal article in that claim 44 particularly recites that the cultured cells express an embryonic stem cell phenotype, including the pluripotent nature of the embryonic stem cell phenotype.

Summarily, claim 44 is believed to be patentably distinguished over the teachings of the Chang 1997 journal article. Claims 45 – 54 are ultimately dependent on patentably distinguished claim 44. Accordingly, withdrawal of the rejection of claims 45 – 54 under 35 U.S.C. § 102(b) based upon the Chang 1997 journal article is respectfully requested. Allowance of claims 44 – 54 is also respectfully requested.

VI. Response to Rejection under 35 U.S.C. § 102(e) based upon U.S. Patents to Petitte et al.

Claims 44 – 54 have been further rejected as being anticipated by U.S. Patent No. 5,340,740; U.S. Patent No. 5,656,479; or U.S. Patent No. 5,830,510, all to Petitte et al. (hereinafter "the cited Petitte patents"). This rejection is respectfully traversed. Initially, it is noted that the cited Petitte patents use a different staging for the embryos, i.e., the EGK staging system instead of the H&H staging system recited in claim 44. Additionally, although the cited Petitte patents do disclose undifferentiated avian cells that express an embryonic stem cell phenotype, the specific isolation of

PGCs later than stage 14 is not recited. As noted above, prior to the disclosure of the present invention, it was not believed that PGCs later than stage 14 (H&H scale) could be used to culture pluripotent undifferentiated avian cells expressing an embryonic stem cell phenotype. Accordingly, claim 44 is believed to be patentably distinguished over the disclosure of the cited Petitte patents.

Claims 45 – 54 are ultimately dependant on patentably distinguished claim 44. Claims 45 – 54 are therefore also believed to be patentably distinguished over the cited Petitte patents. Accordingly, withdrawal of the rejection of claims 45 – 54 is respectfully requested. Allowance of claims 45 – 54 is also respectfully requested.

VII. Response to Rejection under 35 U.S.C. § 102(e) based upon U.S. Patent No. 6,156,569.

The Patent Office has rejected claims 44 – 54 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,156,569 to Ponce de Leon et al. (hereinafter "the Ponce de Leon '569 patent"). See Official Action, page 11, paragraph 11. According to the Patent Office, the Ponce de Leon '569 patent teaches:

> [I]solating PGCs isolated from cells of stage XIV embryos. The cells were cultured with complete medium, LIF, FGF, IGF and SCF for at least 25 days (citation omitted). The PGCs were capable of creating a chimeric chicken which is a phenotype of ES cells. PGCs isolated from stage XIV are equivalent to PGCs isolated later than stage 14 as claimed because PGCs isolated from stage XIV and XIV have the same structure and function.

Official Action at page 11.

The Patent Office asserts that "avian PGCs collected from an avian embryo 'later than stage 14' as claimed does not bear patentable weight because it does not distinguish the structure or function of the PGCs within the culture from those taught by Ponce de Leon". Id. This rejection is respectfully traversed.

Applicants initially wish to point out that the Ponce de Leon '569 patent discloses the use of stage XIV PCGs, and as such, is believed to differ substantially

from PGCs isolated later than stage 14. Stage XIV occurs in the first few hours before gastrulation.

Furthermore, applicants respectfully submit that the isolation of PGCs from a later than stage 14 embryo is believed to be patentably distinguished in the present invention. Prior to the disclosure of the present invention it was believed that it was not possible to obtain pluripotent embryonic stem cells from avian primordial germ cells from an embryo later than stage 14. This, coupled with the ease of isolation provided by using later embryos, is believed to patentably distinguish claim 44 over the disclosure of the Ponce de Leon '569 patent. Accordingly, withdrawal of the rejection of claim 44 based on the Ponce de Leon '569 patent is respectfully requested and allowance of claim 44 is also respectfully requested. It appears that the Patent Office is impermissibly "reading out" one of the elements of the claimed invention by refusing to recognize the distinction between a PGC isolated from a stage XIV embryo and a PGC isolated from a stage 14 embryo.

Claims 45 – 54 believed to be distinguished from the Ponce de Leon '569 patent in view of their dependency of patentably distinguished claim 44. Withdrawal of the rejection of claims 45 – 54 based upon the Ponce de Leon '569 patent is respectfully requested. Allowance of claims 45 – 54 is also respectfully requested.

VIII. Response to First Remaining Obviousness-Type Double Patenting Rejection

Claims 44 – 54 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 3, 13, 19, and 23 of co-pending U.S. patent application Serial No. 08/446,021 (hereinafter "the '021 application"). See paragraph 12, page 12 of the Official Action. This rejection is respectfully traversed.

It is respectfully submitted that claim 44 recites the isolation of primordial germ cells from an avian embryo later than stage 14 (H&H) and culturing the same to form a culture of undifferentiated avian cells expressing an embryonic stem cell phenotype. This is believed to be in marked contrast to the disclosure of somatic tissue-specific stem cells in the '021 application. Accordingly, for the reasons set

forth hereinabove and incorporated here by reference, claim 44 is believed to patentably distinguished over the disclosure of the '021 application. Accordingly, withdrawal of the rejection of claim 44 is respectfully requested.

Claims 45 – 54 are believed to be patentably distinguished over the cited U.S. patent application in view of their dependency of patentably distinguished claim 44. Accordingly, withdrawal of the provisional obviousness type double-patenting rejection of claims 45 – 54 is respectfully requested. Allowance of claims 44 – 54 is also respectfully requested.

IX. Response to Second Remaining Obviousness-Type Double Patenting Rejection

Claims 44 – 54 have been subjected to a second provision obviousness-type double patenting rejection based upon claims 21 – 27 of co-pending U.S. patent application Serial No. 09/094,176. See paragraph 13, pages 12 and 13 of the Official Action. This rejection is respectfully traversed. Applicants respectfully submit that the specific recitation of the use of primordial germ cells isolated from an avian embryo later than stage 14 in the culture as claimed in claim 44 is not disclosed in the claims 21 – 27 of the '176 application. Rather, these claims are directed to a method of introducing a DNA sequence into an in ovo embryo using a cell expressing an embryonic stem cell phenotype. But the unexpected characteristic of the presently claimed culture, namely that primordial germ cells isolated from an avian embryo later than stage 14 (H&H) can be cultured as pluripotent embryonic stem cells, is believed to patentably distinguish current claim 44. Accordingly, withdrawal of this rejection of claim 44 is respectfully requested.

Claims 45 – 54 are ultimately dependent on patentably distinguished claim 44 and are believed to be distinguished from the disclosure of noted claims of the '176 application based on this dependency. Accordingly, withdrawal of the rejection of claims 45 – 54 based on cited claims of the '176 application is respectfully requested. Allowance of claims 45 – 54 is also respectfully requested.

X. Response to Third Remaining Obviousness-Type Double Patenting Rejection

Claims 44 – 54 have been subjected to an obviousness-type double patenting rejection based upon claims 1 and 8-10 of the Petitte '740 patent in view of the Chang 1997 journal article. See paragraph 15, pages 13 and 14 of the Official Action. This rejection is respectfully traversed. While claims 1 and 8-10 of the subject application do claim a sustained culture of undifferentiated avian cells having an ES cell phenotype and methods of making such culture, the proposed combination of these claims and the Chang 1997 reference do not disclose the use of primordial germ cells isolated from an avian embryo later than stage 14 to form a culture comprising undifferentiated avian cells expressing an embryonic stem cell phenotype, as recited in claim 44. Accordingly, the proposed combination does not disclose each and every element of the claimed invention. Therefore, it is respectfully submitted that a prima facie case of obviousness is not supported by the proposed combination. Accordingly, withdrawal of this rejection of claim 44 is respectfully requested. Allowance of claim 44 is also respectfully requested.

Claims 45 – 54 are dependent upon patentably distinguished claim 44. Claims 45 –54 are believed to be patentably distinguished from the proposed combination based upon this dependency. Accordingly, withdrawal of this rejection of claims 45 – 54 is respectfully requested, and allowance of claims 45 – 54 is also respectfully requested.

XI. Response to Fourth Remaining Obviousness-Type Double Patenting Rejection

Claims 44 – 54 have been rejected under the doctrine of obviousness-type double patenting as being unpatentable over claim 1 of the Petitte et al. '470 patent or claim 1 of the Petitte et al. '510 patent in view of the Chang 1997 journal article. The proposed combination of claim 1 the Petitte et al. '470 patent or the Petitte et al. '510 patent and the Chang 1997 journal article do not disclose each and every element of currently pending claim 44. Particularly, there is no disclosure of the use of primordial germ cells isolated from an embryo after stage 14 in the culture of

sustained undifferentiated avian cells expressing a pluripotent embryonic stem cell phenotype. Accordingly, a prima facie case of the obviousness of claim 44 is not believed to be established. Withdrawal of this rejection is respectfully requested. Allowance of claim 44 is also respectfully requested.

Claims 45 – 54 are dependent upon patentably distinguished claim 44. Claims 45 –54 are believed to be patentably distinguished from the proposed combination based upon this dependency. Accordingly, withdrawal of this rejection of claims 45 – 54 is respectfully requested, and allowance of claims 45 – 54 is also respectfully requested.

XII. Response to Fifth Remaining Obviousness-Type Double Patenting Rejection

Claims 44 – 54 have been subjected to an obviousness-type double patenting rejection over claims 1-12 of the Ponce de Leon '569 patent in view of the Chang 1997 journal article. Applicants respectfully note that the Ponce de Leon '569 patent is not commonly owned with the subject application and thus an obviousness-type double patenting rejection is not believed to be appropriate. Applicants now elect to respond to the rejection upon the assumption that a rejection under 35 U.S.C. § 103 was intended.

The proposed combination of the Ponce de Leon '569 patent and the Chang 1997 journal article do not disclose each and every element of the present claim 44. Particularly, there is no disclosure of a sustained culture of undifferentiated avian cells expressing a pluripotent embryonic stem cell phenotype using PGCs isolated from a later than stage 14 embryo in the culture. Accordingly, applicants respectfully submit that a prima facie case of the obviousness of claim 44 has not been made. Withdrawal of this rejection of claim 44 is therefore respectfully requested. Allowance of claim 44 is also respectfully requested.

Claims 45 – 54 are dependent upon patentably distinguished claim 44. Claims 45 –54 are believed to be patentably distinguished from the proposed combination based upon this dependency. Accordingly, withdrawal of this rejection of claims 45 –

54 is respectfully requested, and allowance of claims 45 – 54 is also respectfully requested.

CONCLUSION

In light of the above Amendments and Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment After Final to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS & WILSON, P.A.

Date: April 28, 2003 By: _____

Arles A. Taylor, Jr.
Registration No. 39,395

Customer No. Bar Code:

25297

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